JACC Vol. 25, No. 2
February 1995:395-402

Coronary Artery Bypass Graft Surgery After Thrombolytic Therapy in the Thrombolysis in Myocardial Infarction Trial, Phase II (TIMI II)

BERNARD J. GERSH, MB ChB, DPhil, FACC,* JAMES H. CHESEBRO, MD, FACC,
EUGENE BRAUNWALD, MD, FACC,† COSTAS LAMBREW, MD, FACC,‡
EUGENE PASSAMANI, MD, FACC,§ RACHEL E. SOLOMON, MPH,§
ALLAN M. ROSS, MD, FACC,‖ RICHARD ROSS, MSc,¶ MICHAEL L. TERRIN, MD,¶
GENELL L. KNATTERUD, PhD¶ AND THE TIMI II INVESTIGATORS#

Rochester, Minnesota; Boston, Massachusetts; Portland, Maine; Washington, D.C.; and Bethesda and Baltimore, Maryland

Objectives. **We examined the results of coronary artery bypass graft surgery after thrombolytic therapy in the Thrombolysis in Myocardial Infarction trial, Phase II (TIMI II) with particular emphasis on patient characteristics, the impact of antecedent percutaneous transluminal coronary angioplasty and morbidity and mortality in certain subgroups.**

Background. **Coronary bypass surgery is frequently used after thrombolytic therapy, but there is relatively little information with regard to early and late outcomes.**

Methods. **We analyzed 3,339 patients enrolled in the TIMI II trial. Bypass surgery was performed in 390 patients (11.7%): 54 (14%) within 24 h after entry into the trial or within 24 h of coronary angioplasty and 336 (86%) between 24 h and 42 days after entry.**

Results. **Perioperative mortality rates were, respectively, 16.7% and 3.9% ($p < 0.001$); perioperative myocardial infarction rates were 5.6% and 6.2%, respectively; and major hemorrhagic events occurred in 74% and 50.9%, respectively ($p = 0.002$). On multivariate analysis, the only independent predictor of perioperative mortality was bypass surgery within 24 h after entry or after coronary angioplasty. Among patients undergoing bypass surgery within 24 h of entry or after coronary angioplasty, the prevalence of multivessel disease (59.1% vs. 77.8%) and use of the internal thoracic artery (18.5% vs. 62.5%) were lower than in the remaining surgical patients. Among the 322 perioperative survivors, the 1-year mortality rate after discharge was only 2.2% and 1.9%, respectively, in the two groups. Only one patient had a documented recurrent myocardial infarction during the first year.**

Conclusions. **The increased mortality rate with bypass surgery after thrombolytic therapy, particularly in patients undergoing operation within 24 h of coronary angioplasty or during the involving phase of infarction, must be balanced against the excellent 1-year prognosis and perioperative survivors, who are in general a group at higher risk of death or recurrent infarction. These data provide a basis for comparison for future studies.**

(J Am Coll Cardiol 1995;25:395-402)

The benefits of thrombolytic therapy in decreasing early mortality after acute myocardial infarction have been demonstrated unequivocally in several large randomized trials (1–5). It has also become clear that late mortality is surprisingly low (6,7), particularly compared with published series antedating the use of thrombolytic therapy (8); but a single unified hypothesis does not explain the strikingly low late mortality. Mechanisms complementing myocardial salvage have been proposed, including the potential for a patent infarct-related artery to have a beneficial effect on ventricular remodeling or electrical stability and to act as a source of future collateral vessels (6,7,9). Stringent selection criteria for thrombolytic therapy may be related to outcome (10), but the frequent use of coronary revascularization after thrombolytic therapy has been suggested as an additional factor contributing to the low late mortality and cardiac morbidity.

In the Thrombolysis in Myocardial Infarction trial, Phase II (TIMI II), the administration of the lytic agent was only one aspect, albeit a crucial one, of an overall therapeutic approach that included coronary revascularization by coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty (11–13) for appropriate clinical indications. The role of coronary angioplasty has been addressed in several randomized and nonrandomized studies (11–15), but there is relatively little information on the early and late outcomes of bypass surgery after thrombolytic therapy other than reports

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota; †Brigham and Women's Hospital, Boston, Massachusetts; ‡Maine Medical Center, Portland, Maine; §National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; ‖George Washington University, Washington, D.C.; and ¶Maryland Medical Research Institute, Baltimore, Maryland. #A list of the TIMI II Investigators appears in Reference 12. This study was supported by grants and contracts from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. It was presented in part at the 63rd Annual Scientific Sessions of the American Heart Association, Dallas, Texas, November 1990.

Manuscript received November 15, 1993; revised manuscript received August 29, 1994, accepted August 31, 1994.

*Present address and address for correspondence: Georgetown University Medical Center, Washington, D.C. 20007.

Address for reprints: TIMI Coordinating Center, Maryland Medical Research Institute, 600 Wyndhurst Avenue, Baltimore, Maryland 21210.

0735-1097/95/$9.50
0735-1097(94)00387-6

documenting the feasibility of the technique during the early postlysis period (16–21). Therefore, we examined the results of bypass surgery after thrombolytic therapy in the TIMI II trial, with particular emphasis on the characteristics of the patients selected for coronary bypass, the impact of antecedent coronary angioplasty and morbidity and mortality in specific subgroups of patients.

Methods

Trial design. The TIMI II trial was designed to evaluate the role and timing of angiography and coronary angioplasty in patients treated intravenously with recombinant tissue-type plasminogen activator (rt-PA) within 4 h after an acute myocardial infarction characterized by ST segment elevation at presentation. The primary comparison of management strategies was based on the occurrence of death or myocardial infarction within 42 days of study entry. Details of the trial design have been published (11–13), including a substudy (TIMI IIA) of patients who underwent angiography and coronary angioplasty (when the coronary anatomy was suitable) immediately. In the TIMI IIB substudy, patients eligible for beta-adrenergic blocking agent therapy were randomly assigned to immediate intravenous administration of metoprolol (started during the rt-PA infusion) followed by oral treatment or deferred oral therapy with metoprolol starting 6 days after rt-PA infusion (22).

Patient population. Between April 11, 1986 and June 30, 1988, 3,339 patients were entered in the TIMI II trial. Of these, 390 underwent coronary bypass within 42 days of enrollment in TIMI II. The population undergoing coronary bypass evaluated in the present analysis includes patients in TIMI II assigned to either protocol-directed catheterization (206 patients) 18 to 48 h after study entry (invasive strategy) or the conservative strategy of catheterization only when clinically indicated (184 patients).

The details of the administration of rt-PA, heparin and aspirin; methods of treatment assignment; and management strategies have been described elsewhere (11–13,22). Risk of unfavorable outcome was assessed on the basis of age, previous myocardial infarction, anterior myocardial infarction, rales, hypotension and tachycardia, atrial fibrillation or flutter, pulmonary edema and cardiogenic shock (11,12,23).

Bypass surgery was recommended in the TIMI II protocol for invasive strategy group patients with a lumen obstruction ≥70% in the left main coronary artery (n = 10) or with coronary anatomy that provided technical obstacles to coronary angioplasty (e.g., distal lesions in a tortuous vessel) in whom bypass surgery was the treatment of choice (n = 87). In the majority of patients in the conservative strategy group, the indications for bypass surgery were based on a combination of anatomic findings and clinical observations (e.g., rest or exercise-induced ischemia in patients with ≥70% lumen obstruction in more than one major artery that was perfusing normally, contracting or hypokinetic myocardium and coronary arteries anatomically unsuitable for coronary angioplasty).

The techniques of anesthesia, coronary bypass and postoperative management were those in use at the individual institutions participating in the study.

Predismissal and follow-up studies. The techniques for measuring rest left ventricular function and for exercise radionuclide ventriculography have been described elsewhere (11–13,24). Coronary angiography was performed using standardized projections. Contrast left ventriculography was performed in the 30° to 35° right anterior oblique projection.

Statistical analysis. Proportions were compared by using standard Z tests (25). Mean values of continuous variables were analyzed by using the Student t test for two-group comparisons. To adjust for multiple testing, two-sided p values between 0.01 and 0.001 were specified as providing some evidence of differences and $p < 0.001$ as providing strong evidence of differences. Data analyses were performed using the SAS statistical software package (26) and a data file established in January 1991. Survival curves were calculated using the methods of Kaplan and Meier (27), and comparisons of these rates were tested using the log rank statistic. Perioperative mortality is presented as the percent of patients who died before hospital discharge or within 30 days of bypass surgery.

Comparisons of event rates adjusted for patient characteristics were made with the Cox proportional hazards model (28) using BioMedical Data Package (BMDP) programs (29).

Results

Patient groups. The 390 patients who underwent bypass surgery were classified into two groups according to when the operation was performed: 54 patients who underwent bypass surgery within 24 h after entry into the trial or within 24 h of coronary angioplasty performed within 42 days of enrollment in TIMI II (group A) and 336 patients who underwent bypass surgery between 24 h and 42 days after entry (group B) (Table 1). Perioperative mortality and morbidity were similar between patients operated on between 24 h and 7 days and between days 8 and 42. Therefore, these patients were combined into a single group for subsequent analyses.

Baseline characteristics. *Clinical variables.* Patients undergoing "emergency" or "urgent" operation (group A) were younger than those undergoing bypass surgery >24 h after study entry or coronary angioplasty (Table 1). The majority of patients in both groups (63% and 74%) undergoing bypass surgery were considered not to be at "low risk" of an adverse outcome.

Cardiac catheterization variables. Preoperative coronary angiography was performed in all 390 patients undergoing bypass surgery (206 of whom were assigned to the invasive strategy) (Table 2). The infarct-related artery was the right coronary artery in 42%, the left anterior descending coronary artery in ~41% and the circumflex coronary artery in 13%. The infarct-related arteries were similar in the two groups (p = 0.83). In

Table 1. Baseline Characteristics, by Timing of Bypass Surgery*

	Overall (n = 390)		Group A: CABG <24 h (n = 54)		Group B: CABG 24 h to 42 days (n = 336)	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
Mean (±SD) age (yr)	59.7 ± 9.5		55 ± 10.8		60.4 ± 9.0†	
Male gender	330	84.6	42	77.8	288	85.7
White race	355	91.0	48	88.9	307	91.4
Not low risk	283	72.6	34	63.0	249	74.1‡
Age ≥70 yr	63	16.2	6	11.1	57	17.0
Prior MI	96	24.6	11	20.4	85	25.3
Anterior MI	197	50.5	27	50.0	170	50.6
Rales ≥⅓ lung field	22	5.6	3	5.6	19	5.6
Hypotension and sinus tachycardia	26	6.7	6	11.1	20	6.0
Atrial fibrillation or flutter	15	3.8	0	0.0	15	4.5
Pulmonary edema	8	2.1	0	0.0	8	2.4
Cardiogenic shock	9	2.3	3	5.6	6	1.8‡
Other risk factors						
Previous angina	275	70.5	38	70.4	237	70.5
Congestive heart failure	15	3.8	1	1.8	14	4.2
Hypertension	172	44.1	22	40.7	150	44.6
Diabetes mellitus	58	14.9	4	7.4	54	16.1
Ongoing chest pain at rt-PA initiation	347	89.0	46	85.2	301	89.6
Treated ≤2 h	115	29.5	14	25.9	101	30.0
Mean (±SD) time from onset of pain to study entry (h)	2.57 ± 0.92		2.53 ± 0.84		2.57 ± 0.93	

*Of the 54 patients (Pts) operated on within 24 h, 22 underwent coronary artery bypass graft surgery (CABG) within 24 h of study entry and 32 within 24 h of attempted percutaneous transluminal coronary angioplasty (PTCA). †$p < 0.001$ between groups A and B. ‡$p = 0.09$ between groups A and B. MI = myocardial infarction; rt-PA = recombinant tissue-type plasminogen activator.

310 patients, the number of vessels diseased was documented; multivessel disease was present in 75% and triple-vessel disease in 28% (Table 2). The distribution of coronary artery disease among patients undergoing bypass surgery in group A was different from that among those operated on later (group B) ($p = 0.018$). Single-vessel disease was present in 41% of the 44 patients in the former group in whom the coronary anatomy was reviewed by TIMI II investigators for the study but in only 22% of patients undergoing bypass surgery after 24 h ($p = 0.008$). The distribution and extent of coronary disease differed strikingly between the patients in the invasive group undergoing bypass surgery and the 1,475 patients assigned to the invasive strategy who did not undergo operation. Of the 1,343 patients in the latter group in whom the number of vessels with ≥60% stenosis was known, only 27% had multivessel disease, and 5% had triple-vessel disease (30).

Clinical status before bypass surgery. Sixty-three percent of patients undergoing bypass surgery had definite or probable angina, and of these, 79% were in Canadian Cardiovascular Society class III or IV. This included patients assigned to the invasive strategy who underwent protocol-directed catheterization and subsequent bypass surgery.

In group A patients (those undergoing bypass surgery within 24 h of study entry or within 24 h of an attempted coronary angioplasty), only 1 (1.8%) of 54 operations was categorized as elective, whereas it was categorized as elective in 66.7% of patients operated on between 24 h and 42 days of study entry. The indications for bypass surgery are presented in Table 3.

The use of intraaortic balloon counterpulsation in TIMI II was documented for patients undergoing bypass surgery during the initial TIMI II hospital period. In group A, 58.5% of patients were treated with intraaortic balloon counterpulsation preoperatively, including 13 of the 14 patients reported to be in shock. In the 24-h to 42-day bypass surgery group, 20% of patients in total were treated with intraaortic balloon counterpulsation during their initial hospital stay.

Preoperative left ventricular function. Preoperative ejection fraction determined by contrast ventriculography was available for 43% of patients with bypass surgery and was >0.50 in 35%, 0.35 to 0.50 in 46% and <0.35 in 19%. Mean ejection fraction was 0.45 ± 0.13 and 0.46 ± 0.12 in groups A and B, respectively. Preoperative ejection fraction from rest radionuclide ventriculography was available for 67% of patients and was >0.50 in 55%, 0.35 to 0.50 in 32% and <0.35 in 13%. Mean ejection fraction with this technique was 0.52 ± 0.15 and 0.51 ± 0.14 in groups A and B, respectively. When the highest value obtained by either technique was used, 48% of patients had an ejection fraction <0.50; but no measurement of ejection fraction was obtained in 69 of the 390 patients.

Table 2. Bypass Surgery in Thrombolysis in Myocardial Infarction Trial, Phase II: Cardiac Catheterization Before Operation

	Overall (n = 390)		Group A: CABG <24 h (n = 54)		Group B: CABG 24 h to 42 days (n = 336)	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
No. of pts with one catheterization before CABG			51		318	
Infarct-related artery*						
RCA	155	42.0	23	45.1	132	41.5
LMCA	4	1.1	1	2.0	3	0.9
LAD	151	40.9	22	43.1	129	40.6
Cx	48	13.0	4	7.8	44	13.8
None	1	0.3	0	0.0	1	0.3
Not identified	10	2.7	1	2.0	9	2.8
No. of vessels with ≥60% stenosis*						
0	5	1.4	0	0.0	5	1.6
1	72	19.5	18	35.3	54	17.0
2	147	39.8	20	39.2	127	39.9
3	86	23.3	6	11.8	80	25.2
Not identified	59	15.9	7	13.7	52	16.3

*Assessed on first cardiac catheterization only. Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; RCA = right coronary artery; other abbreviations as in Table 1.

Coronary artery bypass surgery. *Perioperative morbidity and mortality.* Overall, 95% of patients received saphenous vein grafts and 62% had internal thoracic artery conduits. Of the 369 patients undergoing bypass of the left anterior descending coronary artery system, 59% had internal thoracic artery conduits. Among patients undergoing bypass within 24 h after coronary angioplasty after entry into the study, the internal thoracic artery was used in only 18.5% compared with 62.5% of patients undergoing bypass between 24 h and 42 days.

Perioperative mortality (defined as death within 30 days or before dismissal from the hospital) was 5.6% overall; it was 16.7% and 3.9% ($p < 0.001$) in groups A and B, respectively (Fig. 1A). In the 32 patients undergoing operation within 24 h of coronary angioplasty, the perioperative mortality rate was 15.6%. Perioperative myocardial infarction was documented in 5.6% and 6.2% ($p = 0.96$) of patients in groups A and B, respectively (Table 4, Fig. 1B). Perioperative mortality rate is presented in Table 5, according to the timing of bypass surgery and the reason for bypass surgery (distinguishing six categories of clinical conditions associated with emergency operation). Bypass surgery within 24 h of a complicated coronary angioplasty is associated with high perioperative mortality rate. Preoperative ejection fraction was not reported in 26 (48%) of the 54 patients undergoing operation within 24 h (group A) and in 92 (27%) of the 336 patients undergoing operation within 24 h to 42 days (group B) ($p = 0.002$), suggesting a degree of ascertainment bias. Among group A patients in whom ejection fraction was ascertained, mortality was 29% in those with an ejection fraction <0.50 as opposed to 0% in 11 patients with an ejection fraction >0.50. Among group B patients with an ejection fraction <0.50, perioperative mortality rate was 6% as opposed to 2.7% in those with an ejection

Table 3. Indications for Bypass Surgery

	Overall (n = 390)		Group A: CABG <24 h (n = 54)		Group B: CABG 24 h to 42 days (n = 336)	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
Elective	225	57.5	1	1.8	224	66.7
Emergency (clinical condition)						
Angina without definite ECG changes	36	9.2	3	5.6	33	9.8
Angina with ECG changes	40	10.3	5	9.3	35	10.4
Persistent chest pain and ST elevation	21	5.4	12	22.2	9	2.7
Other (includes complications from PTCA)	68	17.4	33	61.1	35	10.4

ECG = electrocardiographic; other abbreviations as in Table 1.

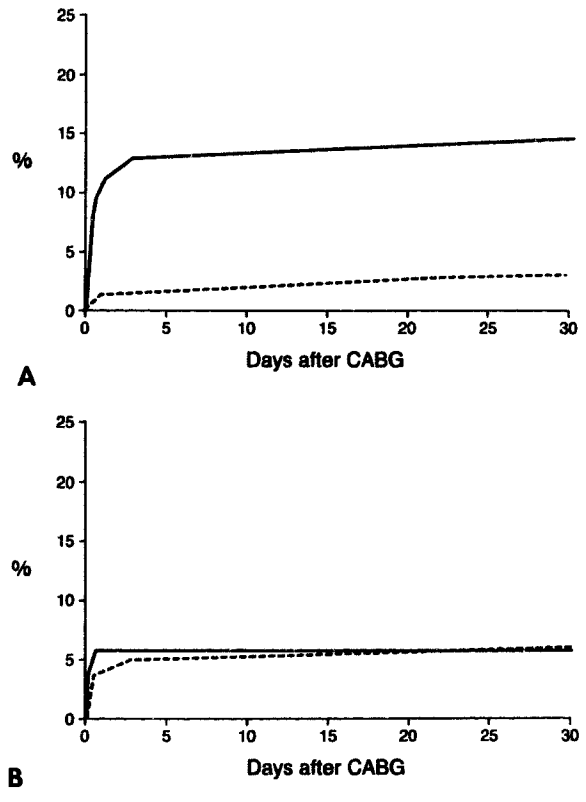

Figure 1. Cumulative Kaplan-Meier mortality curves (**A**) and cumulative recurrence of infarction (**B**) from date of coronary artery bypass graft surgery (CABG) to 30 days. **Solid line** = patients undergoing operation within 24 h of entry into the study or after coronary angioplasty; **dashed line** = patients undergoing operation between 24 h after entry and 42 days.

fraction >0.50. In patients with an ejection fraction <0.35, perioperative mortality rate was 50% and 10.8% in groups A and B, respectively.

Major surgical hemorrhagic events (defined as a blood loss of ≥5 g/dl) occurred in 40 patients (74.1%) operated on within 24 h of study entry or coronary angioplasty and in 171 patients (50.9%) undergoing bypass surgery within 24 h to 42 days of study entry (p = 0.002) (31). Mean (±SD) units transfused were 4.8 ± 4.4 U for the 53 patients in group A and 3.5 ± 3.0 U for 270 patients in group B (p = 0.006) undergoing bypass surgery during the initial TIMI II hospital period.

Late events. Among the 322 perioperative survivors, there were only 7 late deaths during the first year, giving rise to 1-year mortality rate after discharge of 2.2% and 1.9% (p = 0.88) in groups A and B, respectively. Only one patient had a documented nonfatal recurrent myocardial infarction during the first year. Complete follow-up data are available for TIMI II patients only through 2 years. In the interval from the end of the first year of follow-up to the beginning of the second year of follow-up, no patients in group A died, and only six patients in group B died.

Adjusted analyses. From the Cox proportional hazards regression models, the only independent predictor of perioperative mortality was the performance of surgery within 24 h after entry into the trial or within 24 h of coronary angioplasty. Other variables examined (none of which was significant) were gender; race; age; anterior infarction; history of previous myocardial infarction, congestive heart failure, hypertension, previous angina or diabetes; and the timing of thrombolytic therapy. No analyses of late events were performed because there were too few late deaths or recurrent infarctions for adjusted analyses.

Discussion

Frequency of bypass surgery after thrombolytic therapy. A recent meta-analysis (32) suggested that for patterns of practice in North America, intravenous thrombolytic therapy for evolving myocardial infarction is associated with a significant (~80%) short-term increase in subsequent coronary revascularization procedures compared with patients receiving con-

Table 4. Bypass Surgery in the Thrombolysis in Myocardial Infarction Trial, Phase II: Events After Operation

	Overall		Group A: CABG <24 h		Group B: CABG 24 h to 42 days	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
Perioperative events*						
Death	22/390	5.6	9/54	16.7	13/336	3.9
MI	24/390	6.2	3/54	5.6	21/336	6.2
Death or MI	37/390	9.5	9/54	16.7	28/336	8.3
Events after the perioperative period through 1 year from CABG†						
Death	7/366	1.9	1/45	2.2	6/321	1.9
MI	1/366	0.3	0/45	0.0	1/321	0.3
Death or MI	7/366	1.9	1/45	2.2	6/321	1.9

*Events through 30 days or hospital discharge for patients in the hospital >30 days. †Events in 1 year after 30 days from coronary artery bypass graft surgery (CABG) or hospital discharge for patients in the hospital >30 days. Other abbreviations as in Table 1.

JACC Vol. 25, No. 2
February 1995:395–402

Table 5. Perioperative Mortality According to Time of Bypass Surgery and Reason for Operation

Reason for Operation	Group A: CABG <24 h			Group B: CABG 24 h to 42 days		
	No. of Pts	Perioperative Deaths		No. of Pts	Perioperative Deaths	
		No.	%		No.	%
Elective	1	0	0.0	224	5	2.2
Emergency (clinical condition)						
Angina without definite ECG changes	3	0	0.0	33	3	9.1
Angina with ECG changes	5	0	0.0	35	1	2.8
Persistent chest pain and ST segment elevation	12	3	25.0	9	0	0.0
Complication of protocol PTCA	18	2	11.1	0	0	—
Complication of nonprotocol PTCA	10	3	30.0	2	0	0.0
Other	5	1	20.0	33	4	12.1

Abbreviations as in Tables 1 and 3.

ventional therapy. The frequency of bypass surgery during the initial hospital stay of patients undergoing thrombolytic therapy for acute myocardial infarction was ~38% in six series totaling 2,076 patients (33). In the Interuniversity Cardiology Institute of The Netherlands Trial, during the first 3 years after dismissal, either bypass surgery or coronary angioplasty was performed in 35% of patients treated with thrombolysis and in 27% of patients treated conventionally (34); 17% of the patients in the TIMI I trial underwent bypass surgery during the first year (compared with 16% in this TIMI II trial), and either bypass surgery or coronary angioplasty had been performed in ~44% at 12 months (35).

These data emphasize current practice trends toward the more frequent use of bypass surgery as one aspect of a comprehensive therapeutic strategy of acute myocardial infarction, with thrombolytic therapy as the first step.

Characteristics of patients undergoing bypass surgery. Of the 54 patients undergoing operation within 24 h of entry into the study or after coronary angioplasty, only 1 patient was categorized as having an elective operation. The remainder had either persistent angina or complications after angioplasty. In contrast, in patients undergoing operation within 24 h to 42 days from entry, ~65% of the procedures were categorized as elective.

As in most surgical series, the majority of patients had severe angina and multivessel disease. In patients randomized to the invasive arm, the operation was carried out in accord with the protocol because of critical coronary obstruction that was not suitable for coronary angioplasty. Among patients in whom ejection fraction data were available, left ventricular dysfunction (ejection fraction <0.50) was present in 65% and 45% of patients by use of contrast ventriculography and radionuclide angiography, respectively.

Specific indications for bypass surgery were not systematically collected in TIMI II, particularly because 67 of 390 patients undergoing bypass surgery underwent operation after the initial hospital period. The data are therefore confined to patients undergoing operation within the initial hospital period. As illustrated in Table 5, among group A patients undergoing bypass surgery, this was due to complications of coronary angioplasty in 30 patients and persistent chest pain with ST segment elevation in 12 patients. Among group B patients undergoing operation within 24 h to 42 days, the majority of operations were considered elective, but specific details are unavailable.

Distribution of coronary artery disease. In TIMI II, as in many other trials of thrombolytic therapy, only patients with ST segment elevation were eligible for inclusion (12,14). In most studies (including TIMI II), patients with ST segment depression as their only presenting electrocardiographic abnormality, a subgroup with a high incidence of multivessel disease (36,37), were excluded. Consequently, in this study, as in other trials of thrombolytic therapy, the prevalence of multivessel and particularly triple-vessel disease is low (7,11). The more frequent and appropriate use of coronary artery bypass surgery in patients with more extensive disease is illustrated by the higher prevalence of multivessel (75%) and triple-vessel (28%) disease in surgically treated patients.

Perioperative morbidity and mortality. In TIMI II, the higher earlier mortality in patients undergoing bypass surgery within 24 h after study entry or after coronary angioplasty is consistent with other reports (38,39) of mortality after emergency procedures and with the greater prevalence of hypotension and cardiogenic shock among these patients. That coronary bypass surgery within 24 h of a complicated coronary angioplasty is associated with a high mortality is not surprising and is consistent with other reports. In a recent analysis of the 1989 experience with coronary angioplasty in the state of California, the mortality rate was 12.0% for patients with acute myocardial infarction who underwent bypass surgery after coronary angioplasty and 5.6% ($p = 0.0001$) among patients with nonacute infarction who underwent operation after coronary angioplasty (40). Kleiman et al. (41) evaluated the mechanisms of early death in patients in the TIMI II trial. Among the 53 patients who died within 18 h of study entry, pump failure was the attributed mechanism in 62%. The

urgency of the surgical procedures could explain the low utilization of the internal thoracic artery as a conduit in this group of patients (20% as opposed to 69% among patients undergoing operation after 24 h).

Acute coronary syndromes increase the risk of coronary angioplasty, probably because of residual mural thrombus associated with plaque rupture (11,14,42). The majority of operations performed within 24 h after coronary angioplasty were related to a complication or an unfavorable result of the procedure. Analysis (43) of complications in the National Heart, Lung, and Blood Institute PTCA Registry from 1985 and 1986 showed that the mortality rate for emergency bypass surgery was 7.9%, which is substantially less than the 15.2% among patients in this study undergoing operation within 24 h after coronary angioplasty. Comparisons of different series have limitations; nonetheless, these data emphasize the risk of bypass surgery for failed coronary angioplasty in postinfarction patients, some of whom will have significant left ventricular dysfunction and multivessel disease.

The TIMI II investigators previously reported (42) that there was an increase in the occurrence of hemorrhagic events associated with invasive procedures after thrombolytic therapy. In the present study, there is no specific data suggesting that thrombolytic therapy was responsible for any differences in the occurrence of hemorrhagic events, but it is likely that among patients undergoing bypass surgery within 24 h of study entry, thrombolytic therapy could have contributed to the occurrence of perioperative hemorrhagic events. Nonetheless, the high morbidity and mortality among patients in this group is most likely the consequence of a greater severity of their initial illness, requiring emergency bypass surgery.

Among patients undergoing bypass surgery later (between 24 h and 42 days after entry), the perioperative mortality rate of 3.9% is still higher than that found in other series of isolated bypass surgery in patients with chronic stable angina (44,45). The explanation most likely is multifactorial and related in part to left ventricular dysfunction in patients with recent myocardial infarction and multivessel disease (37,46,47). Moreover, the adverse effect of left ventricular dysfunction on operative mortality during the early postinfarction period was emphasized by Hochberg et al. (48). Perioperative mortality rates in patients who had an ejection fraction <0.50 were 19%, 18% and 11% in those undergoing bypass surgery within 3, 4 and 5 weeks after infarction, respectively, and 6% in those undergoing bypass surgery >5 weeks after infarction.

Bypass surgery and late mortality. It would appear that the TIMI surgical population was, in the main, a group with severe coronary disease on the basis of the prevalence of left ventricular dysfunction, multivessel disease, severe angina occurring early after infarction and failure of or unsuitability for coronary angioplasty. Moreover, 24.6% of the patients in the study had a history of myocardial infarction antedating the TIMI infarction, which is considerably higher than the 14% documented among the 3,339 patients in the overall TIMI II trial (49). A history of previous myocardial infarction is an important predictor of an adverse prognosis after thrombolytic therapy (50). It is thus encouraging to note the very low incidence of late events—only six deaths and one recurrent myocardial infarction at 1 year in perioperative survivors. This is similar to that reported for the overall TIMI II trial of 3,339 patients (49), in which mortality from 6 weeks to 1 year was 2.2% and the rate of reinfarction was 2.6%.

Conclusions. The TIMI II study provides detailed data for >390 patients undergoing bypass surgery within 6 weeks of thrombolytic therapy. The high mortality in patients undergoing operation within 24 h of coronary angioplasty or during the evolving phase of infarction is emphasized. In patients undergoing bypass surgery between 24 h and 42 days after entry, the mortality rate of 3.2% is increased compared with that in other series of patients with chronic stable angina, but this must be balanced against the excellent 1-year prognosis in perioperative survivors, who were, in general, a group at high risk of death or recurrent infarction. These observations cannot necessarily be extended to all patients undergoing bypass surgery after myocardial infarction (with or without thrombolytic therapy), but the data provide a basis for comparison with future studies.

References

1. Gruppo Italiano per lo Studio della Streptochinase Nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–401.
2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
3. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet 1988;2:525–30.
4. AIMS Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:545–9.
5. Simoons ML, van der Brand M, de Zwaan C, et al. Improved survival after early thrombolysis in acute myocardial infarction: a randomized trial by the Interuniversity Cardiology Institute in the Netherlands. Lancet 1985;2:578–81.
6. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? [Editorial]. Circulation 1989;79:441–4.
7. Califf RM, Topol EJ, Gersh BJ. From myocardial salvage to patient salvage in acute myocardial infarction: the role of reperfusion therapy. J Am Coll Cardiol 1989;14:1382–8.
8. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331–6.
9. Van de Werf F. Discrepancies between the effects of coronary reperfusion on survival and left ventricular function. Lancet 1989;1:1367–8.
10. Pfeffer MA, Moyé LA, Braunwald E, et al. Selection bias in the use of thrombolytic therapy in acute myocardial infarction. JAMA 1991;266:528–32.
11. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI II A results. JAMA 1988;260:2849–58.
12. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial. N Engl J Med 1989;320:618–27.
13. Rogers WJ, Baim DS, Gore JM, et al. Comparison of immediate invasive,

delayed invasive, and conservative strategies after tissue-type plasminogen activator: results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II-A trial. Circulation 1990;81:1457–76.

14. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–8.
15. Baim DS, Diver DJ, Feit F, et al. Coronary angioplasty performed within the Thrombolysis in Myocardial Infarction II study. Circulation 1992;85:93–105.
16. Wilson JM, Held JS, Wright CB, et al. Coronary artery bypass surgery following thrombolytic therapy for acute coronary thrombosis. Ann Thorac Surg 1984;37:212–7.
17. Rodewald G, Mathey D, Krebber HJ. Bypass surgery following thrombolytic therapy. Z Kardiol 1985;74 Suppl 6:143–6.
18. Messmer BJ, von Essen R, Minale C, et al. Intracoronary thrombolysis and early bypass surgery for acute myocardial infarct: five years' experience. Thorac Cardiovasc Surg 1986;34:1–4.
19. Salem BI, Gowda S, Haikal M, Leidenfrost R, Cox JL, Ferguson T. Early percutaneous transluminal coronary angioplasty or coronary bypass surgery following thrombolytic treatment of acute myocardial infarction. Chest 1987;91:648–53.
20. Petrovich JA, Wellons HA Jr, Schneider JA Kauten JR, Mikell FL, Taylor GJ. Revascularization after thrombolytic therapy for acute myocardial infarction: an analysis of 573 patients. Ann Thorac Surg 1988;46:163–6.
21. Kereiakes DJ, Topol EJ, George BS, et al. Favorable early and long-term prognosis following coronary bypass surgery therapy for myocardial infarction: results of a multicenter trial. Am Heart J 1989;118:199–207.
22. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred β-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B study. Circulation 1991;83:422–37.
23. Hillis LD, Forman S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) phase II co-investigators. J Am Coll Cardiol 1990;16:313–5.
24. Zaret BL, Wackers FJT, Terrin ML, et al. Assessment of global and regional left ventricular performance at rest and during exercise after thrombolytic therapy for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II study. Am J Cardiol 1992;69:1–9.
25. Snedecor GW, Cochran WG. Statistical Methods. 6th ed. Ames (IA): Iowa State Univ. Press, 1967.
26. SAS Institute Incorporated. 1985 SAS Users Guide, Basic Statistics, Version 5. Cary (NC): SAS Institute Incorporated, 1985.
27. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
28. Hosmer DW Jr, Lemeshow S. Applied Logistic Regression. New York: Wiley, 1989.
29. Dixon WJ. BMDP Statistical Software Manual. Berkeley (CA): Univ. of California Press, 1985.
30. Chaitman BR, Thompson B, Wittry MD, et al. The use of tissue-type plasminogen activator for acute myocardial infarction in the elderly: results from thrombolysis in myocardial infarction phase I, open label studies and the thrombolysis in myocardial infarction in phase II pilot study. The TIMI Investigators. J Am Coll Cardiol 1989;14:1159–65.
31. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II trial. Ann Intern Med 1991;115:256–65.
32. Naylor CD, Jaglal SB. Impact of intravenous thrombolysis on short-term coronary revascularization rates. JAMA 1990;264:697–702.
33. Schaff HV. The role of bypass surgery in acute myocardial infarction. In: Gersh BJ, Rahimtoola SH, editors. Acute Myocardial Infarction. New York: Elsevier, 1990:386–97.
34. Simoons ML, Vos J, Tijssen JG, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 1989;14:1609–15.
35. Dalen JE, Gore JM, Braunwald E, et al. Six- and twelve-month follow-up of the Phase I Thrombolysis in Myocardial Infarction (TIMI) trial. Am J Cardiol 1988;62:179–85.
36. Schulman SP, Achuff SC, Griffith LSC, et al. Prognostic cardiac catheterization variables in survivors of acute myocardial infarction: a five year prospective study. J Am Coll Cardiol 1988;11:1164–72.
37. Petriu A, Castañer A, Sanz GA, et al. Angiographic findings 1 month after myocardial infarction: a prospective study of 259 survivors. Circulation 1982;65:1099–105.
38. Naunheim KS, Kesler KA, Kanter KR, et al. Coronary artery bypass for recent infarction: predictors of mortality. Circulation 1988;78 Suppl I:I-122–8.
39. Naunheim KS, Fiore AC, Wadley JJ, et al. The changing profile of the patient undergoing coronary artery bypass surgery. J Am Coll Cardiol 1988;11:494–8.
40. Ritchie JL, Phillips KA, Luft S. Coronary angioplasty: statewide experience in California. Circulation 1993;88:2735–43.
41. Kleiman NS, Terrin M, Mueller H, et al. Mechanisms of early death despite thrombolytic therapy: experience from the Thrombolysis in Myocardial Infarction Phase II (TIMI II study). J Am Coll Cardiol 1992;19:1129–35.
42. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro J. Insights into the pathogenesis of acute ischemic syndromes. Circulation 1988;77:1213–20.
43. Holmes DR Jr, Holubkov R, Vlietstra RE, et al. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. J Am Coll Cardiol 1988;12:1149–55.
44. Gersh BJ, Califf RM, Loop FD, Akins CW, Pryor DB, Takaro TC. Coronary bypass surgery in chronic stable angina. Circulation 1989;79 Suppl I:I-46–59.
45. Rahimtoola SH, Fessler CL, Grunkemeier GL, Starr A. Survival 15 to 20 years after coronary bypass surgery for angina. J Am Coll Cardiol 1993;21:151–7.
46. Jones RN, Pifarré R, Sullivan HJ, et al. Early myocardial revascularization for postinfarction angina. Ann Thorac Surg 1987;44:159–63.
47. Dawson JT, Hall RJ, Hallman GL, Cooley DA. Mortality in patients undergoing coronary artery bypass surgery after myocardial infarction. Am J Cardiol 1974;33:483–6.
48. Hochberg MS, Parsonnet V, Gielchinsky I, Hussain SM, Fisch DA, Norman JC. Timing of coronary revascularization after acute myocardial infarction: early and late results in patients revascularized within seven weeks. J Thorac Cardiovasc Surg 1984;88:914–21.
49. Williams DO, Braunwald E, Knatterud G, et al. One-year results of the Thrombolysis in Myocardial Infarction Investigation (TIMI) Phase II trial. Circulation 1992;85:533–42.
50. Mueller HS, Cohen LS, Braunwald E, et al. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction: analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, Phase II. Circulation 1992;85:1254–64.